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Imatinib mesylate in the treatment of gastrointestinal stromal tumour

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Imatinib mesylate is a selective and potent small-molecule inhibitor of tyrosine kinases, including Kit, platelet-derived growth factor receptor, and the BCR–Abl fusion protein. Kit plays an important role in gastrointestinal stromal tumours (GISTs) and is one of the most exciting therapeutic targets discovered so far. Clinical trials have consistently shown the dramatic efficacy of imatinib mesylate in patients with GIST. This article will review the development and pharmacology of this small-molecule inhibitor and summarise the clinical trials of imatinib mesylate for the treatment of GIST. Although imatinib mesylate has significantly improved the outcomes of most patients with advanced GIST, unanswered questions remain: what is the role of imatinib mesylate in the pre- and postoperative settings? What is the mechanism of the antitumour activity of imatinib? How do you manage patients whose tumours are refractory to imatinib mesylate?

Keywords: clinical trial, gastrointestinal stromal tumour, imatinib mesylate, Kit, sarcoma, targeted therapy

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1. Introduction

1.1 Clinical features of gastrointestinal stromal tumour

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the gastrointestinal (GI) tract, and the majority of GISTs express the Kit receptor (stem cell factor receptor, CD117), as shown by immunohistochemical analysis [1]. However, ~ 4% of GISTs with otherwise typical clinicopathological and cytogenetic features do not express detectable Kit protein [2]. GISTs account for ~ 2, 14 and 0.1% of all stomach cancers, small intestine tumours and colon cancers, respectively, with an annual incidence of ~ 20 cases/million inhabitants [3]. The median age at diagnosis is ~ 58 years. [1] In the 1940s, GISTs were often diagnosed as smooth muscle tumours of the GI tract (GI leiomyosarcoma, leiomyoblastoma and leiomyoma) but advances in histopathology later provided ultrastructural evidence that GISTs were distinct from smooth muscle tumours.

Surgery is the mainstay of therapy for patients with GIST whose primary lesion is deemed resectable by an experienced surgical oncologist. Before the introduction of imatinib mesylate, patients with an inoperable GIST had limited therapeutic options. Gottlieb *et al.* [4] observed that leiomyosarcomas originating from the GI tract did not respond as well to doxorubicin as did those arising from other organ systems. More regimens were tried but patients with GIST had response rates of < 10%. A recent trial of temozolomide in patients with confirmed GIST showed no response in 17 of the 17 patients, many of whom had tumours that had failed to respond to other chemotherapeutic agents [5]. Imatinib is now the standard of care for those patients who are not surgical candidates. It should be noted that some Kit-negative GISTs contain imatinib-sensitive *kit* or *PDGFRA* mutations and, therefore, patients with Kit-negative GISTs should not, *a priori*, be denied imatinib therapy [2].

At present, radiation therapy has little role in the management of this disease. Only scant published data on this topic are available, mostly in the form of anecdotal and case reports. Shioyama *et al.* [6] reported a case of unresectable retroperitoneal metastasis of GIST, which was durably controlled by radiotherapy combined with arterial chemotherapy and immunotherapy. A case of the use of adjuvant radiotherapy for GIST of the rectum was reported by Pollock *et al.* [7]. At 2 years after the completion of this postoperative radiotherapy, the patient remained disease free. Crosby *et al.* [8] reported 10 patients with GIST of the small intestine who were treated with radiotherapy, 2 pre- and 8 postoperatively. The duration of response, however, was not reported.

1.2 Kit as a therapeutic target

Kit is a Type III transmembrane tyrosine kinase receptor in the same family as platelet-derived growth factor receptor (PDGFR), FLT3, and colony-stimulating factor-1 receptor. Kit expression has been described in haematopoietic stem cells, mast cells, endothelial cells, ovarian cells, melanocytes and interstitial cells of Cajal. Furthermore, Kit is expressed in most GISTs, although a small minority show more focal staining in as few as 5 – 20% of tumour cells [9]. Hirota *et al.* [10] initially described gain-of-function mutations of *kit* in five GISTs, and later it was found that > 85% of GISTs have gain-of-function mutations in the *kit* gene [11].

In the presence of ligand or an activating mutation, Kit has been shown to promote cell survival, proliferation, and cell cycle progression through its downstream signalling pathways. Thus, the Kit receptor emerged as an attractive target for therapy in GIST tumours, whose prognosis and management have been limited in the past.

2. Chemistry

In search of kinase inhibitors, Novartis Pharmaceuticals manufactured a series of ATP mimetics. The compounds of the 2-phenylaminopyrimidine class were found to effectively inhibit PDGFR. These initial compounds were the starting point for the development of a series of molecules with increasing inhibitory effect on tyrosine kinases, as well as improved oral bioavailability and solubility in water. Methyl group substitution at position 6 was found to enhance kinase inhibition; further enhancement was achieved when a benzamide group was added to the phenyl ring of the parent molecule. In addition to PDGFR inhibition, imatinib mesylate inhibited Abl and Kit tyrosine kinases [12], thus becoming the lead molecule for clinical development. The addition of *N*-methylpiperazine increased the oral bioavailability of imatinib mesylate and solubility in water. Initially, imatinib mesylate showed potent *in vitro* and *in vivo* inhibition of BCR-Abl transformed cells in chronic myelogenous leukaemia. Now, imatinib mesylate has been evaluated in Phase I – III clinical trials for the treatment of GIST, a tumour known to be mainly driven by the Kit receptor tyrosine kinase.

3. Pharmacodynamics

The proposed major target of imatinib mesylate in GIST cells is the Kit tyrosine kinase receptor, which is composed of extracellular and intracellular domains. The extracellular domains correspond with exons 2 – 9 on the *kit* gene. The ligand-binding domain is exons 2 – 5, the dimerisation domain is exons 6 – 7, and the function of exons 8 – 9 is unknown. The intracellular domain corresponds with exons 11 – 19 on the *kit* gene. The intra-cellular juxtamembrane domain is exon 11. This domain plays a critical role in auto-inhibiting active Kit. In the active conformation, the juxtamembrane domain is extended away from the kinase domains, allowing them to achieve an active conformation. However, in the auto-inhibited conformation, the juxtamembrane domain inserts between the kinase lobes of the intracellular Kit protein. This insertion sterically hinders the A-loop of the kinase, forcing it to act as a pseudosubstrate of the kinase domain [13]. Moreover, mutations in exon 11 confer constitutive activation of the Kit receptor, as the juxtamembrane domain is unable to auto-inhibit the receptor. The effectiveness of imatinib has been demonstrated with receptors containing exon 11 mutations as well as exon 13 (tyrosine kinase domain 1). The ATP binding site is exons 12 – 14, the kinase insert is exon 15, and the phosphotransferase activity domain is exons 16 – 19. Mutations in the *kit* gene seen in GISTs are most commonly found on exons 9, 11, 13 and 17. Imatinib mesylate binds to the ATP binding site of Kit, encoded by exon 13 [11].

When activated by mutation or by its ligand, stem cell factor (Steel Factor; SCF), the Kit receptor undergoes homodimerisation and subsequent autophosphorylation of its tyrosine residues at positions 567, 569, 702, 719, 728 and 934. These phosphorylated tyrosines bind SH2 signalling proteins. SH2 proteins dock to these phosphorylated tyrosines, beginning the second messenger cascade. Specifically, PI-3 kinase docks to position 719, Src kinase to 567 and 569, PLC to 728, Grb2 to 702, and Grb7 to 934 [13].

Imatinib mesylate is thought to displace ATP from its binding site on the intracellular domain of the Kit receptor, preventing autophosphorylation and downstream signalling. Thus, imatinib mesylate abrogates the signalling required for the tumourigenic phenotype in Kit-expressing GIST cells. In the authors' laboratory, complete inhibition of SCF-stimulated autophosphorylation of wild-type *kit* is achieved at concentrations of ≥ 1 µM imatinib mesylate. In addition, gain-of-function mutations of *kit* at the juxtamembrane segment are inhibited by similar concentrations [12].

4. Pharmacokinetics and metabolism

The pharmacokinetics of imatinib mesylate are similar in patients with CML and GIST [14]. Imatinib mesylate has an oral bioavailability of > 97% in oral solution or capsule form [15]. Once absorbed, it binds avidly to serum proteins and reaches peak concentrations in the serum 4 h after

Table 1. Toxicity associated with imatinib mesylate therapy in the US–Finland Phase II trial of 147 patients with advanced gastrointestinal stromal tumour (n = 147).

Toxic effect	Any Grade (%)	Grade 3 or 4 (%)
Fluid retention	74.1	1.4
Nausea	52.4	1.4
Diarrhoea	44.9	2.0
Myalgia or musculoskeletal pain	39.5	0
Fatigue	34.7	0
Rash	30.6	2.7
Headache	25.9	0
Abdominal pain	25.9	0.7
Flatulence	21.8	0
Vomiting	12.9	0.7
Haemorrhage	12.2	4.8
Tumour haemorrhage	2.7	2.7
Upper GI tract bleeding or perforation	3.4	2.7
Dyspepsia	10.9	0
Increased lacrimation	9.5	0
Anaemia	8.8	2.0
Loose stools	8.2	0
Taste disturbance	8.2	0
Neutropenia	6.8	4.8
Abdominal distention	5.4	0
Abnormal liver-function results	5.4	2.7
Leucopoenia	4.8	1.4
Arthralgia	4.1	0
Paresthesia	4.1	0
Oesophageal reflux	4.1	0
Pruritus	4.1	0
Pain (in an extremity)	3.4	0
Blurred vision	3.4	0
Photosensitivity	2.7	0

Adapted from [14].
GI: Gastrointestinal.

administration (4 – 5 and 2 – 3 μg/ml for a 600 and 400 mg dose, respectively) [16]. Imatinib mesylate crosses the blood–brain barrier and results in a 38 ng/ml concentration in the cerebral spinal fluid after a dose of 400 – 600 mg/day [16]. The area under the concentration–time curve is 37.5 and 63.6 μg/h/ml for 400 and 600 mg doses, respectively. Drug accumulation of 1.5- to 3-fold occurs after daily dosing, with a steady-state reached within 1 week [17]. Approximately 13% of the drug is excreted in the urine, whereas most is metabolised in the liver by the cytochrome P450 (CYP) isoenzyme, CYP 3A4. The major metabolite of imatinib mesylate is *N*-desmethyl-imatinib (CGP-74588), and its concentration is ~ 17% of that of imatinib mesylate at steady-state conditions. This metabolite has been shown to have comparable activity to imatinib *in vivo*. After a given dose, 5.6% of imatinib mesylate and 2.2% of *N*-desmethyl-imatinib are eliminated in the urine over a 24-h period. The half-life of imatinib mesylate is ~ 25 h, whereas that of its metabolite is 89 h.

Because imatinib mesylate is hepatically metabolised by CYP 3A4, drugs that are administered with it may undergo changes in their pharmacokinetics, and vice versa. For example, ketoconazole, a broad spectrum antifungal agent, was shown to increase patients' exposure to imatinib mesylate when co-administered [15]. Furthermore, rifampicin increased blood levels of imatinib mesylate. Conversely, imatinib mesylate increased the exposure of patients to simvastatin, a

Table 2. Summary of response, overall survival and progression-free survival.

Study	N	OR (%)	CR (%)	PR (%)	SD (%)	PD (%)	OS (%)	TTP	PFS (%)
van Oosterom *et al.* [22]	36	53	0	53	36	11	–	–	–
von Mehren *et al.* [23]	147	63	0	63	19	12	–	72 weeks (median)	–
Verweij *et al.* [32]	27	71	4	67	18	11	–	–	73 (1 year)
Rankin *et al.* [26]	746								
400 mg/day		48	3	45	–	–	78 (2 years)	–	50 (2 years)
800 mg/day		48	3	45	–	–	73 (2 years)	–	53 (2 years)
Verweij *et al.* [32]	946								
400 mg/day		50	5	45	32	13	69 (2 years)	–	44 (2 years)
800 mg/day		54	6	48	32	9	74 (2 years)	–	50 (2 years)

CR: Complete response; N: Number of patients; NA: Data not available; OR: Objective response; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TTP: Time to progression.

3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor [18]. Moreover, several other pharmaceuticals used by cancer patients, such as alprazolam, acetominophen, clindamycin, clonazepam, cortisol, ethinyl oestradiol and verapamil, may cause toxic effects when administered with imatinib mesylate [18]. Recent studies have also shown *in vitro* synergism between imatinib mesylate, other tyrosine kinase inhibitors, and cytotoxic chemotherapeutics [19].

5. Clinical trials in gastrointestinal stromal tumour

5.1 Phase I studies

The initial Phase I studies of imatinib mesylate were conducted in patients with chronic myeloid leukaemia (CML). The first Phase I trial of imatinib mesylate was performed between June 1998 and May 2000 at three participating study centres [20]. A total of 83 patients with CML in the chronic phase, in whom treatment with IFN-α had failed, were successively assigned to 1 of 14 doses in the range of 25 – 1000 mg/day. The primary end point of this dose escalation study was the safety and tolerability of imatinib mesylate in patients with chronic-phase CML. Doses of this drug were administered orally once-daily, except for the 800 and 1000 mg doses, which were divided into two daily doses. Toxicity was minimal in this study and included nausea, myalgias, oedema and diarrhoea. A maximal tolerated dose was not defined, and imatinib mesylate was found to have significant antileukaemic activity [20].

A single-patient pilot study confirmed the efficacy of imatinib mesylate in GIST. This first patient to be treated with imatinib mesylate was a woman of 50 years of age with chemotherapy-resistant, metastatic GIST who received imatinib mesylate 400 mg/day, starting in March 2000. This patient's tumour had previously been documented to express the Kit receptor (CD117) and was subsequently found to encode a mutation in exon 11 of the *kit* gene. Response was evaluated objectively, using 18-fluorodeoxyglucose positron emission tomography (PET) and computed tomographic radiography. The patient's tumour remained stable after 1 year of therapy, with only mild GI side effects. Serial tumour biopsies revealed myxoid degeneration after only 4 weeks of treatment [21].

A Phase I study of imatinib mesylate in GIST was conducted in three centres of the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (**Table 2**) [22]. The goal of this trial was to identify the dose-limiting side effects of imatinib mesylate in patients with metastatic GIST. Initially, this trial was designed for patients with any advanced soft tissue sarcoma, including GIST, but ultimately, 36 of the 40 patients enrolled had advanced GIST. Between August 3 and December 21, 2000, the patients received either imatinib mesylate 400 mg/day, or 300, 400 or 500 mg b.i.d. The maximum tolerated dose of imatinib mesylate was judged to be 400 mg b.i.d, owing to unacceptable toxicity at the 500 mg b.i.d. dose, which included Grade 3 nausea/vomiting, oedema and dyspnoea. Although not the primary end point, a partial response rate of 53% was reported [22].

5.2 Phase II studies

These encouraging results, as well as the experience of using imatinib mesylate in patients with CML, led to the rapid deployment of several Phase II and III studies of imatinib mesylate in GIST. The initial trial, designated as the US–Finland trial [14], was a multi-centre, open-label, randomised, Phase II clinical trial of imatinib mesylate in patients with unresectable or metastatic, Kit-expressing GIST. Between July 2000 and April 2001, 147 patients were randomly assigned to receive imatinib mesylate 400 or 600 mg/day p.o. This study had a crossover design: patients receiving 400 mg/day whose tumours progressed, but who were otherwise in good clinical condition, were eligible to increase the dose to 600 mg/day. After a median follow-up of 41 weeks, imatinib mesylate was shown to be effective and to have minimal toxicity, with 54%

of patients having a partial response and another 28% demonstrating stable disease. Although there were no complete responses, only 14% of patients exhibited disease progression. Equivalent response rates were seen in the two treatment arms, but this Phase II study was not adequately powered to distinguish a difference in efficacy between the 400 and 600 mg doses [14].

At a median follow-up of 24 months, 63% of patients in the US–Finland trial had a partial response, 19% had stable disease, and 12% had confirmed tumour progression (**Table 2**). The median time to progression was 72 weeks, and the median survival had yet to be reached. The response rates did not differ significantly between the two doses, although there was a trend towards a higher response rate at the 600 mg dose (65 versus 62%) [23].

The above results were confirmed with another Phase II trial performed by the EORTC Soft Tissue and Bone Sarcoma Group (**Table 2**). The goal of this study was to assess the activity of imatinib mesylate in advanced and/or metastatic GIST at the highest feasible dose of 400 mg b.i.d. A total of 27 patients with GIST were enrolled on this trial. Side effects were mild-to-moderate, and the most common included anaemia, periorbital oedema, skin rash, fatigue, nausea, granulocytopenia and diarrhoea. Response rates were similar to those in the US–Finland Phase II trial: 4, 67, 18 and 11% for complete response, partial response, stable disease and disease progression, respectively. At 1 year, 73% of patients were free from disease progression [24].

5.3 Phase III studies

Two Phase III studies were conducted almost simultaneously by two large consortia. One was the North American Sarcoma Intergroup study S0033, consisting of the US cooperative oncology groups (Southwest Oncology Group, Cancer and Leukaemia Group B, and the Eastern Cooperative Group) as well as the National Cancer Institute of Canada Sarcoma Group (**Table 2**). The primary aim of this study was to assess the impact of imatinib mesylate dose (400 versus 800 mg/day) on survival; secondary aims were to evaluate response rates and confirm the tolerability of imatinib mesylate therapy in patients with GIST. Between December 15, 2000, and September 1, 2001, 746 patients from 57 institutions were enrolled. Patients randomised to receive the 400 mg/day dose were allowed to cross over to the 800 mg/day dose if they had radiographic evidence of progressive disease (RECIST). Early results of this trial were presented at the American Society of Clinical Oncology (ASCO) annual meeting in 2003 [25]. At a median follow-up of 14 months, overall response rates were similar in both arms: 43 and 41% at the 400 and 800 mg dose, respectively [25]. There was no difference in progression-free or overall survival between dose levels. The most recent update of this trial was presented at the 2004 ASCO meeting [26]. Median overall survival had not been reached in either arm after a median follow-up of 25.6 months, and there continued to be no significant differences between the two arms in regards to progression-free and overall survival. Progression-free survival rate estimates at 2 years are 50 versus 53% for the 400 and 800 mg arms, respectively. Survival estimates at 2 years are 78 versus 73% for the 400 and 800 mg arms, respectively. However, of the 106 patients who crossed over to the higher dose after having progressive disease on the 400 mg/day dose, 7% had a partial response and 32% had stable disease, indicating that patients can benefit from a higher dose after their disease progresses on 400 mg/day.

The EORTC Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group conducted the second Phase III trial of imatinib mesylate (**Table 2**). Between February 2001 and February 2002, 946 patients with GIST were randomised to receive imatinib mesylate at a dose of either 400 mg/day or 400 mg b.i.d. This trial was powered to detect a 10% difference in progression-free survival rates, with objective response to treatment as a secondary end point. At a median follow-up of 760 days (~ 25 months), 56% of patients on the once-daily arm had progressed, compared with only 50% of patients on the twice-daily arm (estimated hazard ratio: 0.82; 95% CI = 0.69 – 0.98; p = 0.026). The benefit in terms of median progression-free survival was an extra 5 months for those patients on the 400 mg b.i.d. arm. A total of 52 (5%) patients achieved a complete response, 442 (47%) patients achieved a partial response, and 300 (32%) patients had stable disease. The median time to best response was 107 days. The significance of this trial is that, although both arms achieved the same induction response, the dose of 400 mg b.i.d. achieved a significantly longer progression-free survival. Overall survival estimates at 1 year are 85 and 86% for the once- and twice-daily arms, respectively. At 2 years, overall survival estimates are 69 and 74% for the once- and twice-daily arms, respectively [27]. As reported earlier, the North American trial did not show a statistically significant difference in progression-free survival, and the reason for this discrepancy is unknown, although one could consider differences in site of *kit* mutation, differences in racial composition between the two studies, and the larger size of the EORTC study.

6. Safety and tolerability

The US–Finland Phase II trial demonstrated that imatinib mesylate was generally well-tolerated. However, virtually every patient had at least some mild or moderate adverse events (Grade 1 or 2) that were attributable to therapy [14]. The most common adverse events were oedema (which was most frequently periorbital), nausea, diarrhoea, myalgia or musculoskeletal pain, fatigue, rash, headache, and abdominal pain (see **Table 1**). Although most of these adverse events were mild or moderate, 21% of patients had serious adverse events (Grade 3 or 4). A few (5%) patients experienced intra-abdominal haemorrhages, [14] which were postulated to be associated with massive tumour cell death induced by this active agent.

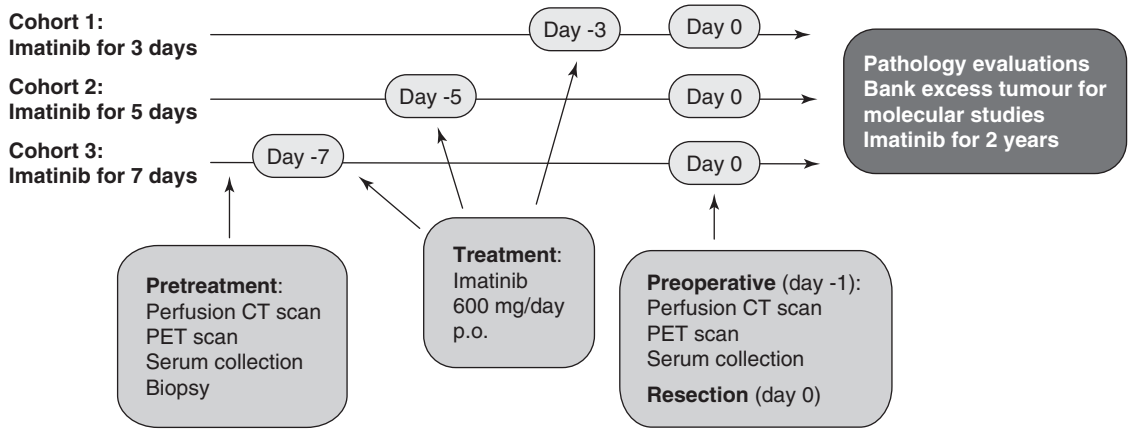

Figure 1. Protocol Schema for MDACC ID03-0023: pre- plus postoperative imatinib for patients with gastrointestinal stromal tumour.

CT: Computed tomography; PET: Positron emission tomography.

The most recent toxicity results of the large Phase III trial conducted by the EORTC Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group were reported at a median follow-up of 760 days (~ 25 months) [27]. Almost all patients in both arms (imatinib 400 mg/day versus twice daily) had some type of side effect – 468 of 472 (99%) patients in the twice-daily arm and 465 of 470 (99%) in the once-daily arm. The most common haematological events were anaemia (879 patients, 93%) and granulocytopenia (395, 42%). Haemoglobin levels fell by a median of 8% compared with initial values in patients on 400 mg/day and by a median of 13% in patients on 800 mg/day. The most common non-haematological side effects were oedema (748, 80%), fatigue (693, 74%), nausea (515, 55%), pleuritic pain (500, 53%), diarrhoea (494, 52%), and rash (345, 37%). Patients on the higher dose of imatinib were more likely to have at least one Grade 3 – 4 side effect (152 [32%] on once-daily treatment compared to 237 [50%] on twice-daily treatment; $p < 0.0001$). Also, patients on the twice-daily arm were more likely to have certain side effects (oedema, anaemia, rash, lethargy, nausea, bleeding, diarrhoea and dyspnoea) compared with those patients on the once-daily arm. However, serious adverse events were reported equally for both arms, 174 patients (37%) for the once-daily arm versus 180 (38%) for the twice-daily arm. Imatinib was the most probable cause of death in 5 (0.5%) patients (2 patients on the once-daily arm, and 3 on the twice-daily arm). In an additional 13 (1%) patients, imatinib could not be completely ruled out as the cause of death. Hepatic toxic events (3 patients) and bleeding (2 patients) were thought to be the cause of death in 5 patients.

Dose reductions were much more likely in patients taking imatinib 400 mg b.i.d. compared with those on the once-daily arm (282 [60%] versus 77 [16%]; $p < 0.0001$). The reason for a dose reduction was more likely to be a non-haematological rather than a haematological toxic effect in either arm. Patients on the higher dose of imatinib were more likely to need a treatment interruption (302 [64%] versus 189 [40%]; $p < 0.0001$), most often from a non-haematological rather than a haematological toxic effect. In summary, imatinib mesylate is safe and generally well-tolerated at doses ≤ 800 mg/day.

7. Pre- and postoperative imatinib in gastrointestinal stromal tumour

An innovative study at The University of Texas MD Anderson Cancer Center (MDACC ID03-0023 [28]) has been designed to gain a better understanding of the radiographic, histological and molecular responses seen when patients with GIST are treated with imatinib mesylate (**Figure 1**) [101]. This trial provides an innovative approach with important biological correlates that may provide insight into the mechanism of action of imatinib in GIST. In ID03-0023, patients with resectable GIST undergo standard surgery followed by adjuvant imatinib mesylate for 2 years [101]. The objectives are: to determine whether imatinib has pro-apoptotic or antivascular antitumour activity in the treatment of patients with GIST; to determine the disease-free survival of patients with resectable GISTs treated with imatinib mesylate preoperatively and continued for 2 years after resection; and to assess the safety and tolerability of imatinib mesylate given to patients with GISTs preoperatively and continued postoperatively.

As presented at the ASCO 2002, tumour metabolic activity by PET scan was completely abrogated by imatinib mesylate in 1 – 3 days in 3 of 4 patients with GIST [28]. In order to understand the early molecular and pathological changes in GIST tumours treated with imatinib mesylate with respect to PET response, imatinib mesylate will be initiated 3, 5 or 7 days prior to surgical resection and after baseline core biopsy.

Tumour vascularity will be evaluated to determine whether imatinib mesylate is an antivascular drug. Imatinib mesylate may inhibit pericyte PDGFR pathways, which may interfere

with pericyte function and result in destruction of tumour neovasculature. Potential antivascular activity will be assessed by two methods: perfusion computed tomography (perfusion CT scan) and laser scanning cytometry (LSC). Perfusion CT will allow the measurement of tumour blood volume, vascular permeability and the rate of tumour perfusion.

LSC allows fluorescence-based quantitative measurements on tissue sections or other cellular preparations at the single-cell level. This will allow measurement of tumour cell apoptosis, microvessel density, and endothelial cell apoptosis [29].

This project is likely to contribute to the understanding of the targets of imatinib mesylate-mediated antitumour activity. Furthermore, this trial will evaluate surrogate markers of anti-angiogenesis and pro-apoptotic therapy to determine whether these correlate with pathological response and inhibition of Kit signalling.

Patients whose GIST has been resected may be eligible for a clinical trial of adjuvant imatinib through the American College of Surgeons Oncology Group (ACOSOG) Z9001 [30]. On this trial, patients with completely resected high-risk GIST are randomised to receive either 1 year of adjuvant therapy with imatinib or placebo. Patients must have a KIT-expressing GIST and must be registered within 70 days of their surgical resection. This study will determine whether postoperative imatinib will improve disease-free survival.

8. Imatinib mesylate-refractory gastrointestinal stromal tumour

If patients have only been treated with imatinib 400 mg/day p.o., the first step would be to increase the dose of imatinib to 800 mg/day p.o. As in the North American Sarcoma Phase III Intergroup study S0033, the EORTC Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Phase III trial found that patients benefited from the higher dose of imatinib after progression on 400 mg/day p.o. Of the 97 evaluable patients in this study on the lower dose arm (400 mg/day) who crossed over to the higher dose arm (800 mg/day), 2 (2%) patients had confirmed partial responses and 30 (31%) patients had stable disease [30]. The appropriate management of metastatic GIST that has not responded or has become resistant to imatinib mesylate even at high doses is not known. Investigators at The University of Texas MD Anderson Cancer Center and other institutions are currently developing new clinical trials to evaluate imatinib mesylate in combination with other agents, as first-line therapy and upon relapse. An ongoing clinical trial for imatinib mesylate-refractory GIST is that of irinotecan 20 mg/m^2/day administered for 5 days, followed by 2 days off, for 2 weeks on a 3-weekly schedule. Clinical trials are in progress of combining imatinib mesylate with oblimersen and single-agent Amgen 706, a small-molecule inhibitor of Kit and the vascular endothelial growth factor receptor. A small number of patients with localised sites of progression, despite continuation of imatinib, have been treated with percutaneous radiofrequency ablation (RFA). Imatinib was continued in this group of nine patients, and the RFA was applied with CT guidance [31]. This approach appears to be a safe and effective treatment for those patients with localised sites of progression. Physicians should be encouraged to refer patients with GIST to centres that have access to these clinical trials. For those patients whose disease becomes refractory to imatinib mesylate and who are not eligible for a clinical trial, palliative therapy, such as hepatic artery embolisation, surgical debulking and intraperitoneal chemotherapy, should be considered.

9. Expert opinion and conclusion

Imatinib mesylate has quickly become the most active targeted, small-molecule therapy in patients with solid tumours. Imatinib mesylate is the first-line agent for metastatic GIST and is currently being evaluated against other tumour types. Several ongoing studies of imatinib mesylate in GIST address the important issues of efficacy of adjuvant therapy, efficacy of neoadjuvant therapy, duration of therapy, safety in the perioperative period, and molecular response measured by PET imaging. The use of imatinib mesylate for treating patients with GIST will be tailored by the final results of these neoadjuvant, adjuvant and metastatic clinical trials and their associated correlative studies.

The identification of imatinib mesylate as an agent to specifically target the critical pathogenetic mechanisms of GIST represents a major advance in the treatment of this disease. The information gained from the success of imatinib mesylate in GIST will enhance drug development for oncology in general, but many challenges lie ahead in the applications of these strategies to other human cancers.

On the basis of studies published in abstract form, it appears that very few patients with metastatic GIST exhibit complete responses to imatinib mesylate therapy, perhaps owing to relatively slow responses or the failure of imatinib mesylate to induce cell death in some cases. The exact cause may be determined by studies in which GIST patients receive imatinib mesylate preoperatively. If indeed imatinib mesylate arrests cell growth but does not induce apoptosis, combination therapy with a proapoptotic agent would be intriguing. If imatinib mesylate has no effect on tumour vasculature, perhaps combining it with an antivascular agent would enhance efficacy.

The mechanisms of primary and acquired resistance to imatinib mesylate are not known and are being actively investigated. It is possible that the site of the mutation on the *kit* gene determines the kinetics of Kit inhibition by imatinib mesylate. Tumours from patients whose disease relapses after an initial response to imatinib mesylate therapy may be undergoing clonal selection for tumour cells encoding a *kit* mutation in an imatinib mesylate-resistant domain, such as the ATP binding site. Alternatively, resistance may develop through the activation of pathways located downstream or in parallel to Kit and therefore not sensitive to inhibition by

imatinib mesylate. Whatever the outcome, this is an amazing opportunity to understand the biological basis of resistance to one of the most successful therapeutic advances in oncology.

It appears that the wild type expression of *kit* is not sufficient to confer the antitumour activity of imatinib mesylate. Thus, inhibiting a normal target may not have antitumour activity if the target does not provide an essential function to the tumour cell. Therefore, identification of molecular abnormalities, which are essential for tumourigenesis will lead to the development of new anticancer therapies.

Understanding diseases, such as GIST, may lay the foundation for understanding the more complex types of human cancer.

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